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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Plunkett
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1643

Appellants: John B. Harley and Judith A. James

Serial No: 08/781,296 Examiner: Mary K. Zeman

Filed: January 13, 1997 Art Unit: 1643

For: *DIAGNOSTICS AND THERAPY OF EPSTEIN-BARR VIRUS IN AUTOIMMUNE DISORDERS*

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Assistant Commissioner of Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 27-40 in the Office Action mailed January 31, 2001, in the above-identified patent application. A Notice of Appeal was filed on July 2, 2001. A Petition for an Extension of Time for four months, up to and including January 2, 2002, and the appropriate fee for a small entity are enclosed. The fee in the amount of $160 for the filing of this Appellants' Brief is also enclosed.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignees, the Oklahoma Medical Research Foundation, Oklahoma City, OK, The Board of Regents of the University of Oklahoma

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Health Science Center, Oklahoma City, OK, and the licensee, JK Autoimmunity, Inc., Oklahoma City, OK.

(2) RELATED APPEALS AND INTERFERENCES

The following related appeal is known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal:

U.S.S.N. 08/475,955 filed June 7, 1995. This is an appeal from the final rejection of claims 1, 2, 5, and 7-11 in the Office Action mailed December 9, 1997 and maintained in the Advisory Action signed on April 23, 1998. A Notice of Appeal was mailed on April 9, 1998. An Appeal Brief was filed August 9, 1998.

(3) STATUS OF CLAIMS ON APPEAL

Claims 27-40 are pending and on appeal. Claims 30-40 have been withdrawn from consideration as allegedly drawn to a non-elected composition, but the language in the office action is confusing, indicating that once product claims are allowable, method claims may be considered. The text of each claim on appeal, as amended, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The pending claims were last amended by the Amendment mailed July 5, 2000.

(5) SUMMARY OF THE INVENTION

The claims are drawn to a group of unique peptides of defined amino acid sequence, up to about 40 amino acids in length and present either in free form or bound to a carrier molecule (claims 27, 29-34), and method of administration thereof to an individual to induce tolerance to EBV-associated immune responses (claims 28, 35-40).

EBV, or Epstein-Barr virus, has been alleged to be a causative agent of a number of different disorders, including various cancers and autoimmune disorders (pages 1-3). The data with respect to lupus, an autoimmune disorder having a variety of different symptoms, typically characterized by the production of antibodies to one's own DNA and proteins such as La and Ro, has been very inconsistent (pages 4-6). Appellants present evidence showing that there is a statistically significant correlation between EBV infection and development of autoimmune disease such as lupus (pages 26-29; 31-46; Figures 7 and 8). Appellants have identified specific peptides present in EBV proteins that can be used to induce autoimmune disease in animals (pages 30-32). Appellants have shown that lupus patients have elevated levels of autoantibodies to these peptides (pages 46-48). This information can be used to make vaccines to EBV which exclude these epitopes and are therefore less likely to cause lupus in those patients who are susceptible to developing lupus (page 8, line 32-page 9, line 2; page 49, lines 25-33; see also

example 8) and to induce tolerance to the epitopes that elicit the immune response (page 24, lines 18-33).

(6) ISSUES ON APPEAL

The issues presented on appeal are

(1) whether claims 28 and 29 should be rejected under 35 U.S.C. §112, first paragraph, as non-enabled.

(2) whether claim 27 should be rejected under 35 U.S.C. §102(e) over U.S. patent No. 5,965,353 to Middeldorp.

(3) whether claim 27 should be rejected under 35 U.S.C. §102(b) over PCT WO 94/06912 to Middeldorp.

(4) whether claims 28 and 29 should be rejected under §103 over U.S. patent No. 5,965,353 to Middeldorp.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. Clearly a rejection of composition claim 27, 30, 31, 32, 33, and 34, drawn to a peptide, on the basis that they are not enabled for a therapeutic use, such as the method of claims 28 and 35-40, where there is a substantial diagnostic use, is improper, as discussed in more detail below. There is no legal basis for this rejection.

Moreover, this would seem to directly contradict the examiner's withdrawal of claims 30-40, as drawn to an invention other than as defined by claims 27-29.

(8) ARGUMENTS

(i) The Invention

The claimed invention is a group of peptides, defined by claims 27 and 29-34, and methods of use, defined by claims 28 and 35-40, based on the discovery that certain epitopes that are shared with viral protein epitopes can elicit an autoimmune disease. The data in the application show the following:

(a) Serum samples from human patients with lupus all contain autoantibodies immunoreactive with the same octapeptide portions of the Sm autoantigen; of these octapeptides, three are bound by autoantibody present prior to presentation with clinical symptoms. (pages 28-29) Immunization of rabbits with one of these octapeptides causes the rabbits to develop a lupus like disorder, with epitope spreading characteristic of human lupus. (pages 30-31, Figures 5 and 6). Immunization of mice with the octapeptide also causes the mice to develop a lupus like disorder, which is genetically linked. (page 31).

(b) Pediatric patients with Lupus all have antibodies to the Epstein-Barr viral capsid antigen. The difference with normal controls is statistically significant to $p < 0.00000001$. The autoantibodies react with specificity to the virus. The evidence strongly supports the theory that EBV infection is required to develop lupus. (pages 32-46).

(c) Lupus patients have elevated levels of antibodies to specific octapeptides (page 46; Figures 3 and 7). The binding patterns are quite distinct when compared to normals without autoimmune disease. (page 47, Table 5, Figures 8D and 8E).

Additional data was submitted in the Declaration under 37 C.F.R. 1.132 of Dr. John Harley mailed January 6, 1999, following an interview with the examiner.

(a) In response to the examiner's concern that the only disorder tested was lupus, the data in the declaration showed an association between EBV and another autoimmune disorder, inflammatory polyarthritis (pages 1-6).

(b) He also stated that they had been able to administer the peptides shown in the studies described in the application to induce lupus like disease, to induce disease in additional animal studies and to induce tolerance. Rabbits were administered peptide to induce anti-Sm autoimmunity. Based on the schedule of administration, some animals developed the disease and other did, indicating that they had been tolerized to Sm BB' (page 6-7).

(c) Development of the disease in animal models, as in humans, has a genetic variable. When thirteen different strains of mice were immunized the same way with the same octapeptide, only six strains showed B cell epitope spreading and development of anti-spliceosomal autoimmunity (page 7-8)

(d) The non-antigenic peptides not only do not induce anti-spliceosomal immunity and indicates that one should be able to use these non-antigenic peptides to interfere with or prevent anti-spliceosomal autoimmunity.

(e) Induction of disease is dose-dependent. Too high or too low of a dose does not induce disease, consistent with high and low zone tolerance, providing further evidence of tolerance induction (page 8).

(f) Induction of disease is dependent on the administration schedule. A single immunization of rabbits with the octapeptide induceds tolerance, not B-cell epitope spreading (page 9).

(g) The antigenic octapeptide can be chemically modified so that no anti-spliceosomal autoantibody is detectable in either mice or rabbits immunized with the modified octapeptide (pages 8-9).

(h) A completely different octapeptide derived from the nRNP A protein was used to induce B cell epitope spreading and spliceosomal autoimmunity in rabbits and in mice. A control "non-antigenic" octapeptide derived from the same protein did not induce B cell epitope spreading or spliceosomal autoimmunity in either rabbits or mice (page 9).

In summary, the appellants have shown:

(a) correlation of two totally different autoimmune diseases, systemic lupus erythematosus and inflammatory polyarthritis, with EBV infection, where the disease course is characterized by autoantibody titers highly reactive with specific octapeptides, B-cell epitope spreading and autoimmunity;

(b) induction of B-cell epitope spreading and autoimmunity by immunization of animals using two totally different octapeptides (one from Sm B/B' and one from nRNP A) as antigens;

(c) induction of B-cell epitope spreading and autoimmunity in different animal species: rabbits, mice and baboons;

(d) induction of tolerance by controlling the dose of the octapeptide administered to the animal;

(e) induction of tolerance by controlling the schedule of administration of the octapeptide to the animal;

(f) induction of tolerance by chemical modification of the octapeptide which is used to immunize the animal; and

(g) induction of tolerance by immunization of the animal to a relatively non-antigenic octapeptide.

Appellants also provide literature evidence that shows that in vitro binding data of epitopes involved in autoimmune-type diseases are predictive of *in vivo* use. Nicholson, et al., Proc. Natl. Acad. Sci. USA 94(17):9279-9284 (1997) was submitted to show that a slightly mutated epitope of the proteolipid protein of myelin acts as an antagonist of the T cell receptor and blocks binding of the epitope in vitro and function *in vivo*. Treatment of the peptide halted the destruction of myelin in mice which is caused by an autoimmune attack on the myelin. Gautam, et al., J. Immunol. 161(1):60-64 (1998) showed that the herpesvirus Saimiri contains small epitopes which when injected into a mouse cause experimental autoimmune encephalomyelitis (EAE) indicating that small epitopes can cause disease. Vandenbarke, et al.,

Immunol. Cell Biol. 76(1):83-90 (1998) showed that vaccinations with epitopes related to EAE and multiple sclerosis caused protective responses to these diseases *in vivo*.

Enclosed with this appeal brief is further evidence showing that methods for inducing tolerance by administration of peptides are known and accepted by those skilled in the art, and that the animal models are predictive of results in humans. These include abstracts as follows:

As of 1995, showing use of peptides to induce tolerance was accepted by those skilled in the art: Mor and Cohen "Vaccines to prevent and treat autoimmune diseases" Int. Arch. Allergy Immunol. 108(4):345-349 (1995); Wraith, "Induction of antigen-specific unresponsiveness with synthetic peptides: specific immunotherapy for treatment of allergic and autoimmune conditions" Int. Arch. Allergy Immunol. 108(4):355-359 (1995).

As of 1998, showing that epitope spreading was verifiable by other groups, Singh and Hahn, "Reciprocal T-B determinant spreading develops spontaneously in murine lupus: implications for pathogenesis" Immunol. Rev. 164:201-208 (1998).

As of 2000-2001, theories appellants based methods on are validated and mechanisms beginning to be understood: Wauben, "Immunological mechanisms involved in experimental peptide immunotherapy of T-cell-mediated diseases" Crit. Rev. Immunol. 20(6):451-469 (2000); Harrison and Hafler, "Antigen-specific therapy for autoimmune disease" Curr. Opin. Immunol. 12(6):704-711 (2000); Mocci, et al., "The role of autoantigens in autoimmune disease" curr. Opin. Immunol. 12(6):725-730 (2000); Riemekasten, et al., "Strong acceleration of murine lupus by injection of the SmD1 (83-119) peptide" Arthritis. Rheum. 44(10):2435-2445 (2001).

(ii) Rejection Under 35 U.S.C. § 112, first paragraph

Claims 28 and 29 were rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The basis of the rejection is that the field of autoimmunity is inherently unpredictable and that data with a single epitope (which does show epitope spreading but not protection against development of autoimmunity) is inadequate to show enablement.

(a) The data demonstrates the application is fully enabling.

This rejection ignores the evidence of record. First, as noted above, data from more than one peptide has been shown to induce B-cell spreading and development of autoimmunity. Second, this has been demonstrated in mice, rabbits and baboons, which are considered to be appropriate animal models for autoimmunity in humans. Third, the data does show development of tolerance: based on dosage; based on schedule of administration; based on administration of non-antigenic peptide; and based on chemical modification of the antigenic peptide.

Literature has been submitted showing that those skilled in the art believe both that animal models are predictive of efficacy in humans, and that *in vitro* binding data is predictive of *in vivo* activity.

(b) Appellants have met the legal requirements under 35 U.S.C. 112

It is not clear if the rejection is being made as lacking utility or lacking enablement or some hybrid thereof.

An invention must have utility. This requirement can be found in U.S.C. § 101 which states," Whoever invents or discovers any new and *useful* process or . . . composition of matter . . .

may obtain a patent . . ." (emphasis added). This requirement is also implicitly found in 35 U.S.C. § 112 which requires the specification to provide a written description for "making and *using*" the claimed subject matter.

Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C. § 112, the standard to be applied is the same. *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'f 1987). The *Maas* court stated, "the issue under 35 U.S.C. § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C. § 101 relating to patentable utility." Any analysis of a claim under 35 U.S.C. § 112, first paragraph relating to the use of the claimed subject matter, need only meet the standards of the utility requirement of 35 U.S.C. § 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement of use.

To meet the utility requirement the invention must simply have a "practical utility" in the "real world sense." (*Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA, 1980)). Any use which gives immediate benefit to the public is sufficient to be a "practical utility". *Id.* at 856. It is clear that for an invention to have "practical utility" it must be operative. However, to fail the utility requirement the claimed subject matter must be "totally incapable of achieving a useful result. ("In short, the defense of non-utility cannot be sustained without proof of total incapacity.").) (*Brooktree Corp v. Advanced Micro Devices. Inc.*, 977 F.2d 1555 (Fed. Cir. 1992). See also *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980). An

assertion of utility is sufficient to meet the utility requirement unless the assertion is "incredible in the light of the art or factually misleading." (*In re Citron*, 325 F.2d 1389 (CCPA, 1963)).

The standard for utility does not change if the subject matter is pharmaceutical or therapeutic in nature. (*In re Chilowsky*, 229 F.2d 457, 461-2 (CCPA 1956)). "Knowledge of pharmacological activity is an obvious benefit to the public. . . . [A]dequate proof of any such activity constitutes a showing of practical utility" (*Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA, 1980)). The Federal Circuit held that adequate proof of a pharmacological activity can be obtained by merely providing *in vitro* data which are suggestive of an activity *in vivo*. (*Cross v. Iizuka*, 753 F.2d 1040 (CAFC, 1985). "Successful *in vitro* testing . . . [will lead to] . . . *in vivo* testing . . . thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility." *Id.* at 1051. Furthermore, data obtained from animal models clearly is adequate proof. *In re Krimmel* 292 F.2d 948 (CCPA, 1961). The *Krimmel* court stated, "one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant contribution to the art even though it may eventually appear that the compound is without value in the treatment of humans." *Id.* at 953.

Future testing in animals and future testing in humans, even if extensive, does not prevent a specification from meeting the utility requirement. The Court stated in *In re Brana*, "Usefulness in Patent law and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." (*In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995)). If the subject matter covered by pharmaceutical inventions requires future research and

development, even after conception and constructive reduction to practice, when then is the utility requirement met? The Federal Circuit has answered this question: "The stage at which an invention in this field becomes useful [i.e. enabled with respect to use requirement] is *well before* it is ready to be administered to humans." (emphasis added) *Id.* at 1568.

The law does not explicitly state what is required to meet the utility requirement for any given pharmacological use because an analysis of utility is a fact based decision. (*Ratheon v. Roper*, 724 F.2d 956). The law is explicitly clear, however, as to what pharmaceutical utility does not require. Pharmaceutical utility does not require human testing (*In re Jolles*, 628 F.2d 1322 (CCPA, 1980); *In re Krimmel*, 292 F.2d 948 (CCPA, 1961); *Cross v. Iizuka*, 753 F.2d 1040 (1985); and *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995)). Pharmaceutical utility does not require animal testing (*In re Krimmel*, 292 F.2d 948 (CCPA, 1961) and *Cross v. Iizuka*, 753 F.2d 1040 (1985)). Pharmaceutical utility does not require a showing of therapeutic safety (*In re Brana* 51 F.3d 1560 (Fed. Cir. 1995) and *In re Irons*, 340 F.2d 974, 978 (CCPA 1965)). Most importantly, pharmaceutical utility does not require a showing of efficacy (See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (1977); I*n re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981)).

Of particular importance is the fact that neither claims 27 and 28 require a specified level of efficacy, nor do they require the cure of any autoimmune disease. The Examiner made it clear

in the Office Action dated March 17, 1999, that "No evidence has been set forth which shows the lessening of any symptom of an autoimmune disease by the administration of a composition of the invention." The Examiner also states, "The specification does not set forth any examples wherein the administration of the elected composition in an accepted animal model is able to successfully "alleviate" an already existing autoimmune disease" and "There are no experiments which challenge vaccinated animals with live unattenuated EBV such that the prevention of the autoimmune disease is shown."

However, Appellants are not required to show or provide the types of data that the Examiner demands. The efficacy or the extent of therapeutic effectiveness is to be addressed at the FDA, not the PTO. The Federal Circuit is clear (see above) that the time that pharmaceuticals are ready for patenting is well before they are ready for use or treatment in a human. There is absolutely no requirement one provide animal model data.

Appellants are required to show that the claimed compounds or methods are likely to have the pharmaceutical utility and the Federal Circuit has indicated that *in vitro* data are sufficient for this if it is "suggestive of an activity *in vivo*." (*Cross v. Iizuka*, 753 F.2d 1040 (CAFC, 1985)).

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g.*, Genentech, Inc. v. Novo Nordisk A/S, 108 F3d at 165,

42 USPQ2d at 1004 (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also In re Fisher, 427 F.2d at 839, 166 USPQ at 24; United States v. Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); In re Stephens, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (M.I.T. v. A.B. Fortia, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of

experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

> The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
>
> Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.
>
> *Id.* at § 2164.05 (emphasis added).

With regard to post-filing art, the CAFC stated in In re Brana, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995), that a post-filing date declaration setting forth test results substantiating utility

"pertains to the accuracy of a statement already in the specification. . . . It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed." An important distinction has been made by the Courts between evidence of the knowledge and ability of those of skill in the art at the time of filing and evidence to prove that statements made in the application are correct. In the former case, of course, only evidence which existed prior to the filing of the application, or evidence that certain knowledge existed at the time of filing, is admissible (In re Hogan, 194 USPQ 527 (CCPA 1977)). In the latter case, any evidence, developed at any time, may be submitted for consideration.

The clearest affirmation of the seasonability of factual evidence developed after the filing date of an application is provided by the Court in In re Marzocchi (169 USPQ 367, 370 (CCPA 1971)). In discussing rejections under 35 USC 112 where an examiner asserts that the unpredictability of the art creates a reasonable doubt as to the accuracy of a particular broad statement (in the application) supporting enablement, the Court states:

> Most often, additional factors, such as the teachings of pertinent references[*], will be available to substantiate any doubts that the asserted scope of enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof.
>
> ***

> Not necessarily *prior* art references, it should be noted, since the question would be regarding the *accuracy* of a statement in the specification, not whether that statement had been made before. [emphasis in the original]
>
> *Id. at 367*

In *In re Wilson* (135 USPQ 442, 444 (CCPA 1962)), the Court agreed that a reference, published after the filing date of the application, was properly cited to show a state of fact. In *In re Langer* (183 USPQ 288, 297 (CCPA 1974)), the Court again noted that later published references "are properly cited for the purpose of showing a fact." In *In re Rainer* (134 USPQ 343, 345 (CCPA 1962)) the Court found no error in the limited use made of a reference published after Appellant's filing date to show a fact. While all of these cases involved publications cited by the Patent Office in support of rejections, the same standard applies to evidence cited by Appellant. See In re Hogan.

Each piece of post-filing art may be evidence of the enablement of one or more element in the claims. Each piece goes to the issue of enablement of the claimed invention as a whole. The post filing art need only display the proposition for which it is submitted. It is not necessary, nor is it required, that each element of the claimed invention be within a single post filing art reference. Each fact and piece of evidence supporting enablement can and should be considered for what it shows. It is improper to require one specific form of evidence while ignoring others. It is the evidence as a whole that must be considered. Elements of the claimed invention

independently described in the post filing art, can cumulatively demonstrate the feasibility of reducing the invention to practice using materials and methods described in the specification and/or known by a skilled artisan as of the time of filing.

Lastly, there is no legal requirement that an inventor have actually reduced the invention to practice prior to filing. MPEP at § 2164.02, *citing* Gould v. Quigg, 822 F.2d 1074 (Fed. Cir. 1987). "The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation." *Id.*

The data provided in the application and verified by the experiments described in the Declaration under C.F.R 1.132 by Dr. Harley clearly indicate that the claimed compounds are likely to have an effect on the course of autoimmune diseases. Autoimmune diseases are associated with the production of antibodies to a variety of epitopes and the use of these epitopes for desensitization or the use of vaccines absent the epitopes is clearly indicated by the *in vitro* data linking the autoantibodies of autoimmune diseases and the epitopes of the claimed subject matter. The present application clearly establishes the connection between the epitopes and the autoimmune diseases of the claims.

Not withstanding the above Appellants have provided a number of references which indicate that the *in vitro* binding data of epitopes involved in autoimmune-type diseases are predictive of *in vivo* use . See also the abstracts enclosed with this Appeal Brief. These clearly show that those skilled in the art believe that the results would be predictive of inducing tolerance generally, not just

to a specific antigen. Indeed, in view of the abundance of evidence showing that immunization with a single octapeptide induces an immune response to many different epitopes on the protein, unrelated to the immunizing peptide, as a result of B-cell epitope spreading, it would make no sense to limit the claims to inducing tolerance to a particular epitope.

(iii) Rejections Under 35 U.S.C. § 102

Claim 27 was rejected under 35 U.S.C. §102(e) over U.S. patent No. 5,965,353 to Middeldorp or under 35 U.S.C. §102(b) over PCT WO 94/06912 to Middeldorp.

Claim 27 is drawn to a peptide composition comprising a peptide having a defined sequence, wherein the peptide is up to about 40 amino acids and is present either in free form or bound to a carrier molecule. The exact language of the claim, which is in a Markush format, is:

A peptide composition comprising a peptide molecule selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:13), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:14), RPQKRPSC (SEQ ID NO:15), QKRPSCIGCKGTHGGTG (SEQ ID NO:16), GTGAGAGARGRGG (SEQ ID NO:17), SGGRGRGG (SEQ ID NO:18), RGGSGGRRGRGR (SEQ ID NO:19), RARGRGRGRGEKRPRS (SEQ ID NO:20), SSSSGSPPRRPPPGR (SEQ ID NO:21), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:22), PDVPPGAI (SEQ ID NO:23), PGAIEQGPA (SEQ ID NO:24), GPSTGPRG (SEQ ID NO:25), GQGDGGRRK (SEQ ID NO:26), DGGRRKKGGWFGKHR (SEQ ID NO:27), GKHRGQGGSN (SEQ ID NO:28),

GQGGSNPK (SEQ ID NO:29), NPKFENIA (SEQ ID NO:30), RSHVERTT (SEQ ID NO:31), VFVYGGSKT (SEQ ID NO:32), GSKTSLYNL (SEQ ID NO:33), GMAPGPGP (SEQ ID NO:34), PQPGPLRE (SEQ ID NO:35), CNIRVTVC (SEQ ID NO:36), RVTVCSFDDG (SEQ ID NO:37), PPWFPPMVEG (SEQ ID NO:38) and combinations thereof, wherein the peptide comprises up to about forty amino acids and is present either in free form or bound to a carrier molecule.

(a) The PCT application does not disclose the claimed peptide.

The claim language is quite clear that the peptide molecule is selected from the group consisting of....specifically named sequences, wherein the peptide comprises up to about forty amino acids. Appellants' Sequence ID No. 24, the sequence in issue, is

PRO GLY ALA ILE GLU GLN GLY PRO ALA

Middeldorp's peptide defined by Sequence ID No. 6 in the PCT application is PRO (430) ASP VAL PRO then

PRO GLY ALA ILE GLU GLN GLY PRO.

Therefore the sequences are not the same. Although appellants use language that allow inclusion of additional amino acids at either end of the peptide, there is no provision for the **deletion** of one of the amino acids, in this case, the terminal ALA required by Appellants' peptide, which is not present in Middeldorp's peptide.

(b) The Middeldorp patent is not prior art to this application.

It appears that there is an error in the published U.S. Patent, since this patent issued in 1999 on the PCT application, discussed above (years after publication of the PCT application corresponding to the present application). SEQ ID NO:6 in the patent does include a terminal ALA. The sequence is discussed at col. 8, lines 54-59, but the only actual sequence is provided in the sequence listing. However, here it is referred to as between positions **430 and 438 of the EBNA-1 fragment 348-470** , which does not correspond to SEQ ID NO:6, which is twelve amino acids long, so it is impossible to know what is actually being referred to.

In fact, it appears that most of the sequence listings in the PCT differ from those in the patent: SEQ ID NO:2 in the PCT is 24 amino acids; it is 20 amino acids in the US patent; SEQ ID NO:3 in the PCT is 31 amino acids; it is 27 amino acids in the US patent; SEQ ID NO:4 in the PCT is 31 amino acids; it is 29 amino acids in the US patent; SEQ ID NO:6 in the PCT application is 12 amino acids; it is 9 amino acids in the US patent (including an ALA at the carboxy terminus, and missing the first four amino acids present in the PCT application.

It is not clear how the U.S. patent can differ so much from the PCT application on which is it based, except that it certainly does not appear to be entitled to the priority date of the filing of the PCT application, at best being entitled to the filing of the sequence listing in the U.S. case, if it is entitled to that date. There is no disclosure in the application of the sequences, other than in the sequence listings. The sequence listing does not match the PCT application.

The present application claims priority to U.S.Serial N. 08/160,604 filed November 30, 1993, now U.S. Patent No. 6,232,522. This patent discloses Ro peptides that are

immunoreactive with autoantibodies from lupus patients. SEQ ID NO:24, the peptide in issue, includes **amino acids 431-438 of the Ro antigen (contrast with the Middeldorp patent which refers to amino acid sequence present in EBV proteins).**. Figures 7A and 7B are the immunoreactivity of octapeptides of the Ro antigen (the sequence of Ro is known; peptides were synthesized beginning with 1-8, 2-9, 3-10, and so forth, for a total of 531 overlapping octapeptides for screening for activity; see col. 20, lines 53-57). The octapeptide of SEQ ID NO:24 is shown in Figure 7A as highly reactive. Accordingly, although the exact sequence is not listed, this sequence was identified as highly reactive in the priority application dated November 30, 1993. Accordingly, even if the US patent were entitled to the filing date of the PCT application (which makes no sense, based on a comparison of the priority document and the issue patent), this application is entitled to priority before the 102(e) filing date of the U.S. patent of May 11, 1994.

(iv) Rejections Under 35 U.S.C. § 103

Claims 28 and 29 were rejected under §103 over U.S. patent No. 5,965,353 to Middeldorp on the basis that Middeldorp employs "the recited peptides in the treatment of EBV-related disease".

(a) Middeldorp is not available as prior art.

As noted above, this application claims priority to U.S.S.N. 08/160,604 filed November 30, 1993. This application clearly discloses immunization of animals to induce lupus in animal models (col. 21-26). As discussed at col. 12, line 64 to col. 34, the peptides are also disclosed

for use in therapy, as pharmaceuticals, and to induce tolerance. Since the available date of the Middeldorp patent is May 11, 1994, it is not available as prior art to the application in issue. Should the examiner assert the PCT application, this would be available only as of its publication date, March 31, 1994, which is also after the priority date of the application on appeal.

(b) Even if Middeldorp were available, it does not make obvious the claims.

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The prior art does not suggest the claimed invention.

Middeldorp describes EBV proteins which it says are useful. Appellants have instead identified peptides derived from autoantigens (Ro, Sm B/B', etc.). There is nothing in Middeldorp that would lead one to identify peptide sequences which are more immunoreactive with autoantibodies, or that could be used to induce autoimmunity or conversely to induce tolerance to the autoantibodies. Middeldorp does not disclose the claimed sequences. Since Middeldorp discloses viral protein sequences, not autoantigen sequences, one skilled in the art

could not extrapolate from Middeldorp to the claimed peptides. Accordingly, Middeldorp does not make obvious the claimed peptides or methods of use.

A prima facie case of obviousness cannot be established by hindsight reconstruction.

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

Middeldorp especially cannot make obvious the methods of use to induce tolerance to an autoantigen, since Middeldorp does not recognize that the EBV proteins may cause autoimmune disease. Middeldorp only discloses methods for vaccinating against EBV using EBV peptides – i.e., they vaccinate with viral peptides to prevent infection by the virus, not to prevent a disease that develops years after infection with a virus. Only by using hindsight reconstruction could one possibly argue that the claimed method was obvious.

(9) SUMMARY

Based on the foregoing, the claimed compositions and methods are both enabled and have utility. The claimed compositions and methods are neither disclosed by nor obvious from the prior art cited by the examiner.

(10) CONCLUSION

Claims 27-29 should be allowed and the case remanded to the examiner for consideration of claims 30-40 with claims 27-29.

Respectfully submitted,

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APPENDIX: Claims as pending on appeal.

27. (twice amended) A peptide composition comprising a peptide molecule selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:13), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:14), RPQKRPSC (SEQ ID NO:15), QKRPSCIGCKGTHGGTG (SEQ ID NO:16), GTGAGAGARGRGG (SEQ ID NO:17), SGGRGRGG (SEQ ID NO:18), RGGSGGRRGRGR (SEQ ID NO:19), RARGRGRGRGEKRPRS (SEQ ID NO:20), SSSSGSPPRRPPPGR (SEQ ID NO:21), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:22), PDVPPGAI (SEQ ID NO:23), PGAIEQGPA (SEQ ID NO:24), GPSTGPRG (SEQ ID NO:25), GQGDGGRRK (SEQ ID NO:26), DGGRRKKGGWFGKHR (SEQ ID NO:27), GKHRGQGGSN (SEQ ID NO:28), GQGGSNPK (SEQ ID NO:29), NPKFENIA (SEQ ID NO:30), RSHVERTT (SEQ ID NO:31), VFVYGGSKT (SEQ ID NO:32), GSKTSLYNL (SEQ ID NO:33), GMAPGPGP (SEQ ID NO:34), PQPGPLRE (SEQ ID NO:35), CNIRVTVC (SEQ ID NO:36), RVTVCSFDDG (SEQ ID NO:37), PPWFPPMVEG (SEQ ID NO:38) and combinations thereof, wherein the peptide comprises up to about forty amino acids and is present either in free form or bound to a carrier molecule.

28. (twice amended) A method comprising administering to a individual a peptide composition comprising a molecule selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3),

GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:13), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:14), RPQKRPSC (SEQ ID NO:15), QKRPSCIGCKGTHGGTG (SEQ ID NO:16), GTGAGAGARGRGG (SEQ ID NO:17), SGGRGRGG (SEQ ID NO:18), RGGSGGRRGRGR (SEQ ID NO:19), RARGRGRGRGEKRPRS (SEQ ID NO:20), SSSSGSPPRRPPPGR (SEQ ID NO:21), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:22), PDVPPGAI (SEQ ID NO:23), PGAIEQGPA (SEQ ID NO:24), GPSTGPRG (SEQ ID NO:25), GQGDGGRRK (SEQ ID NO:26), , GKHRGQGGSN (SEQ ID NO:28), GQGGSNPK (SEQ ID NO:29), NPKFENIA (SEQ ID NO:30), RSHVERTT (SEQ ID NO:31), VFVYGGSKT (SEQ ID NO:32), GSKTSLYNL (SEQ ID NO:33), GMAPGPGP (SEQ ID NO:34), PQPGPLRE (SEQ ID NO:35), CNIRVTVC (SEQ ID NO:36), RVTVCSFDDG (SEQ ID NO:37), PPWFPPMVEG (SEQ ID NO:38), and combinations or immunogenic portions thereof, wherein the peptide comprises up to about forty amino acids and is present either in free form or bound to a carrier molecule, and wherein the composition is in a pharmaceutically acceptable carrier for administration of the composition in an amount and mode of administration effective to induce tolerance to EBV-associated immune responses.

29. (amended) The composition of claim 27 wherein the peptide molecules are in a pharmaceutically acceptable carrier for administration of the composition in an amount and mode of administration effective to induce tolerance to EBV-associated immune responses wherein the composition is in a pharmaceutically acceptable carrier for administration of the

composition in an amount and mode of administration effective to induce tolerance to EBV-associated immune responses.

30. The peptide molecules of claim 27 immobilized to a solid support.

31. The peptide molecules of claim 27 labeled with a detectable label.

32. The peptide molecules of claim 30 immobilized to multiwell plates.

33. The peptide molecules of claim 30 immobilized to a gel suitable for affinity chromatography.

34. The peptide molecules of claim 27 bound by autoantibodies in patients characterized by specific disorders.

35. (amended) A method for determining the likelihood that an individual has or will develop an autoimmune disorder comprising screening their antibodies for reactivity with a peptide molecule selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:13), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:14), RPQKRPSC (SEQ ID NO:15), QKRPSCIGCKGTHGGTG (SEQ ID NO:16), GTGAGAGARGRGG (SEQ ID NO:17), SGGRGRGG (SEQ ID NO:18), RGGSGGRRGRGR (SEQ ID NO:19), RARGRGRGRGEKRPRS (SEQ ID NO:20), SSSSGSPPRRPPPGR (SEQ ID NO:21), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:22), PDVPPGAI (SEQ ID NO:23), PGAIEQGPA (SEQ ID NO:24), GPSTGPRG (SEQ ID NO:25), GQGDGGRRK (SEQ

ID NO:26), DGGRRKKGGWFGKHR (SEQ ID NO:27), GKHRGQGGSN (SEQ ID NO:28), GQGGSNPK (SEQ ID NO:29), NPKFENIA (SEQ ID NO:30), RSHVERTT (SEQ ID NO:31), VFVYGGSKT (SEQ ID NO:32), GSKTSLYNL (SEQ ID NO:33), GMAPGPGP (SEQ ID NO:34), PQPGPLRE (SEQ ID NO:35), CNIRVTVC (SEQ ID NO:36), RVTVCSFDDG (SEQ ID NO:37), PPWFPPMVEG (SEQ ID NO:38) and combinations or immunogenic portions thereof, wherein the peptide comprises up to about forty amino acids and is present either in free form or bound to a carrier molecule.

36. The method of claim 35 wherein the peptide molecules are immobilized to a solid support.

37. The method of claim 35 wherein the peptide molecules are labeled with a detectable label.

38. The method of claim 36 wherein the peptide molecules are immobilized to multiwell plates.

39. The method of claim 35 wherein the peptide molecules are immobilized to a gel suitable for affinity chromatography.

40. The method of claim 35 wherein the peptide molecules are bound by autoantibodies in patients characterized by specific disorders.

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1: Int Arch Allergy Immunol 1995 Dec;108 (4):345-9

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Vaccines to prevent and treat autoimmune diseases.

Mor F, Cohen IR.

Department of Cell Biology, Weizmann Institute of Science, Rehovot, Israel.

The current therapy for human autoimmune disease is based on nonselective immunosuppression achieved by corticosteroids or cytotoxic drugs. This form of therapy is toxic and frequently not effective in curing the disease. The study of experimental autoimmune disease models indicates that the pathogenic population of immune cells is restricted in terms of T-cell receptor gene usage and peptide epitopes recognized in the self-antigens. The recent developments in understanding of the pathophysiology of autoimmune disease point to the crucial role of the pathogenic T cell, the autoantigenic peptide, and the major histocompatibility complex molecules as well as the regulatory T-cell population in the disease process. The purpose of this review is to describe the use of vaccines to prevent and treat autoimmune disease. Encouraging results in animal models using vaccines based on the pathogenic T cell or the autoantigen have prompted the design of novel and selective immune-based therapies for human autoimmune disease.

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Induction of antigen-specific unresponsiveness with synthetic peptides: specific immunotherapy for treatment of allergic and autoimmune conditions.

Wraith DC.

Department of Pathology and Microbiology, Bristol University School of Medical Sciences, UK.

Current drug-based therapies for autoimmune and allergic conditions are non-specific and often associated with severe side effects. Recent advances in our knowledge of how T cells see antigens points to an improved strategy. T lymphocytes recognise processed forms of antigen which can be mimicked by synthetic peptides designed and built in the laboratory. It is clear from recent work that these synthetic peptides, when given systemically in solution, induce a state of hyporesponsiveness in naive T cells thereby specifically preventing a subsequent immune response. Moreover systemic administration of soluble peptides can inhibit ongoing immune responses. Taken together this new information offers great promise for future development of antigen-based drugs for the treatment of autoimmune and allergic diseases.

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Reciprocal T-B determinant spreading develops spontaneously in murine lupus: implications for pathogenesis.

Singh RR, Hahn BH.

Department of Medicine, University of California, Los Angeles 90095-1670, USA. rasingh@med1.medsch.ucla.edu

Recent work from several laboratories has shown that, in contrast to the widely held notion that one autoimmune disease is caused by one or a few related autoantigenic determinants, autoimmunity is fundamentally a continuously evolving process. The autoimmune responses shift, drift and diversify with time not only to other determinants in the original antigen but also to other antigens. We have described a form of determinant spreading--reciprocal T-B determinant spreading--where the induction of first T cells by peptides from an autoantibody molecule could lead to help provided to a variety of B cells displaying a cross-reactive version of the original determinant. The response spreads in this way by reciprocal T-B stimulation until large cohorts of T and B cells have expanded. Such spontaneous expansion must be important in clinical disease, since tolerance induction to a limited set of T-cell determinant peptides derived from an anti-DNA antibody VH region delayed the appearance of IgG anti-dsDNA antibodies and onset of lupus nephritis in the NZB/NZW F1 mouse model of systemic lupus erythematosus. Understanding the diversification patterns in autoimmune responses has enormous implications in developing peptide-targeted therapies.

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Immunological mechanisms involved in experimental peptide immunotherapy of T-cell-mediated diseases.

Wauben MH.

Institute of Infectious Diseases & Immunology, Department of Immunology, Utrecht University, The Netherlands.

Current therapies for autoimmune diseases and allergy involve general immune suppression. However, the ideal therapy should specifically eliminate or modulate the (auto)pathogenic immune response or, alternatively, it should reinforce the regulatory response, without affecting the overall function of the immune system. This could be achieved by antigen-specific immunotherapy. Antigen-specific immunotherapy has received ample attention in the last years, and several clinical trials attempting to treat autoimmune diseases or allergy through the induction of antigen-specific tolerance or immune deviation have been conducted, albeit with varying success. Recent advances in our understanding of peripheral tolerance, regulatory T cells, and routes of antigen administration have resulted in better insight into the different working mechanisms and potential target molecules of antigen-specific immunotherapy. The experimental animal models and new technological developments force the pace in the development of these immunotherapies. The current review addresses several aspects of antigen-specific immunotherapies and focuses on the mechanisms of the different approaches in experimental autoimmune and allergy models.

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Antigen-specific therapy for autoimmune disease.

Harrison LC, Hafler DA.

Autoimmunity and Transplantation Division, The Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Parkville 3050, Australia. harrison@wehi.edu.au

The application of self-antigens as therapeutic tools is validated in inbred animal models of autoimmune disease. Mechanisms of antigen-induced tolerance (apoptosis, anergy, regulatory T cells and immune deviation) are being clarified in relation to the properties of antigens and the modes and routes of their delivery. Mucosa-mediated tolerance remains the predominant mode of antigen-specific therapy but awaits demonstration of clinical efficacy in human autoimmune disease.

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1: Curr Opin Immunol 2000 Dec;12 (6):725-30

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The role of autoantigens in autoimmune disease.

Mocci S, Lafferty K, Howard M.

Division of Autoimmune Disease, Corixa, 301 Penobscot Drive, Redwood City, CA 94603, USA.

Many autoantigens have been identified in human patients and in rodent models. In numerous experimental settings, these autoantigens or related autoreactive lymphocytes can transfer autoimmunity. Although autoreactivity spreads to new epitopes during the course of disease, single-epitope-specific therapies show considerable efficacy in multi-epitope-induced models of autoimmunity. These observations may indicate that epitope-specific therapies operate at the level of regulating mechanisms of immune tolerance rather than exerting a direct effect on autoreactive T lymphocytes.

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1: Arthritis Rheum 2001 Oct;44(10):2435-45

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Strong acceleration of murine lupus by injection of the SmD1(83-119) peptide.

Riemekasten G, Kawald A, Weiss C, Meine A, Marell J, Klein R, Hocher B, Meisel C, Hausdorf G, Manz R, Kamradt T, Burmester GR, Hiepe F.

Department of Rheumatology and Clinical Immunology, Charite University Hospital, Humboldt University of Berlin, Germany. gabriela.riemekasten@charite.de

OBJECTIVE: The mechanisms of IgG anti-double-stranded DNA (anti-dsDNA) antibody induction are incompletely understood. We recently demonstrated a high prevalence of autoantibodies to the C-terminus of SmD1 in patients with systemic lupus erythematosus (SLE) that was closely associated with anti-dsDNA reactivity. The aim of the present study was to analyze the influence of the SmD1 C-terminus on the generation of pathogenic anti-dsDNA antibodies in a murine model of SLE. METHODS: Female lupus-prone prenephritic (NZB x NZW)F1 mice (NZB/NZW mice) as well as female control BALB/c, NZW, and (BALB/c x NZW)F, mice (CWF1 mice) were subcutaneously injected with keyhole limpet hemocyanin (KLH)-coupled SmD1(83-119). Controls received injections of recombinant SmD1 (rSmD1), KLH-rSmD1, KLH-coupled randomized peptide of SmD1(83-119), ovalbumin, or saline. Animals were monitored for survival and proteinuria and for levels of plasma creatinine, urea, and autoantibodies. In addition, histologic examinations were performed and T cell responses against SmD1(83-119) peptide and rSmD1 protein were determined in SmD1(83-119)-treated and -untreated NZB/NZW mice. RESULTS: Immunization with KLH-SmD1(83-119), but not with control peptide, significantly accelerated the natural course of lupus in NZB/NZW mice, with premature renal failure and increased development of anti-dsDNA antibodies. Control strains of mice remained healthy, with no relevant anti-SmD1(83-119) antibodies

detectable even after immunization. In contrast to findings in control mice, a T cell response against SmD1(83-119) was already present in unmanipulated NZB/NZW mice, and this response was further amplified after immunization. CONCLUSION: The SmD1 (83-119) peptide can influence the pathogenic anti-dsDNA response in the NZB/NZW murine lupus model. The data suggest that an SmD1(83-119)-specific T cell response is critical. Therefore, modulation of these autoantigen-specific T cells by tolerance induction may provide a therapeutic approach to specific immunosuppression in lupus.

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US 6232522B1

(12) **United States Patent**
Harley et al.

(10) **Patent No.: US 6,232,522 B1**
(45) **Date f Patent: *May 15, 2001**

(54) **NON-HUMAN ANIMAL MODEL FOR SYSTEMIC LUPUS ERYTHEMATOSIS**

(75) Inventors: **John B. Harley**; **Judith A. James**; **R. Hal Scofield**, all of Oklahoma City, OK (US)

(73) Assignee: **Oklahoma Medical Research Foundation**, Oklahoma City, OK (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **08/160,604**

(22) Filed: **Nov. 30, 1993**

Related U.S. Application Data

(63) Continuation-in-part of application No. 07/867,819, filed on Apr. 13, 1992, now abandoned, which is a continuation-in-part of application No. 07/648,205, filed on Jan. 31, 1991, now abandoned, which is a continuation-in-part of application No. 07/472,947, filed on Jan. 31, 1990, now abandoned.

(51) **Int. Cl.**[7] **C07K 5/00**; A61K 38/00; C12N 15/85

(52) **U.S. Cl.** **800/9**; 514/2; 530/387.1; 530/403; 530/387.2; 435/325; 435/335; 435/375; 435/352; 435/7.2; 435/555; 800/11

(58) **Field of Search** 435/172, 375, 435/7.2, 325, 335, 352, 355; 424/185.1, 9; 530/328, 330, 387.9, 387.1, 403, 387.2; 800/9, 11

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(List continued on next page.)

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(57) **ABSTRACT**

A specific method has been developed to produce an autoimmune response and resulting clinical symptoms for a particular disease process. Peptides or other structures derived from an autoantigen and which are bound by auto antibody or T cell receptors are identified and used to induce an immune response. This immune response evolves into an autoimmune response directed against the other portions of the protein from which the peptide was derived. Subsequently, clinical manifestations may appear that are also found in the clinical illness. selected from the group including viruses, bacteria, fungi, parasites, rickettsia, plasmids, and insects which contains a structure or a peptide sequence that is similar to a structure or peptide sequence that has been identified by the method of claim 1 to the extent that it is bound by one of the group selected from antigen specific B cell surface receptors, and antigen specific T cell receptors.

13 Claims, 9 Drawing Sheets

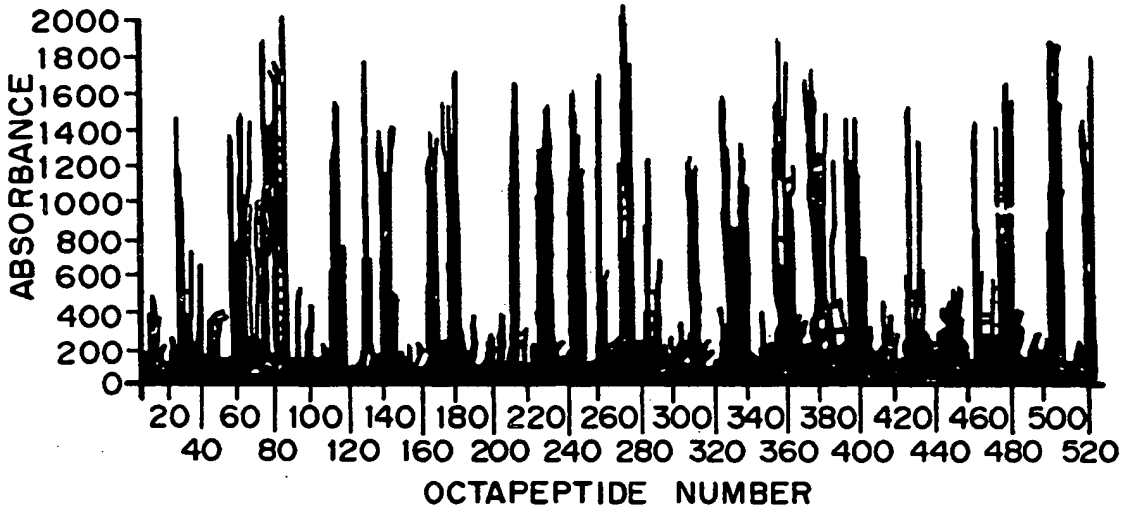
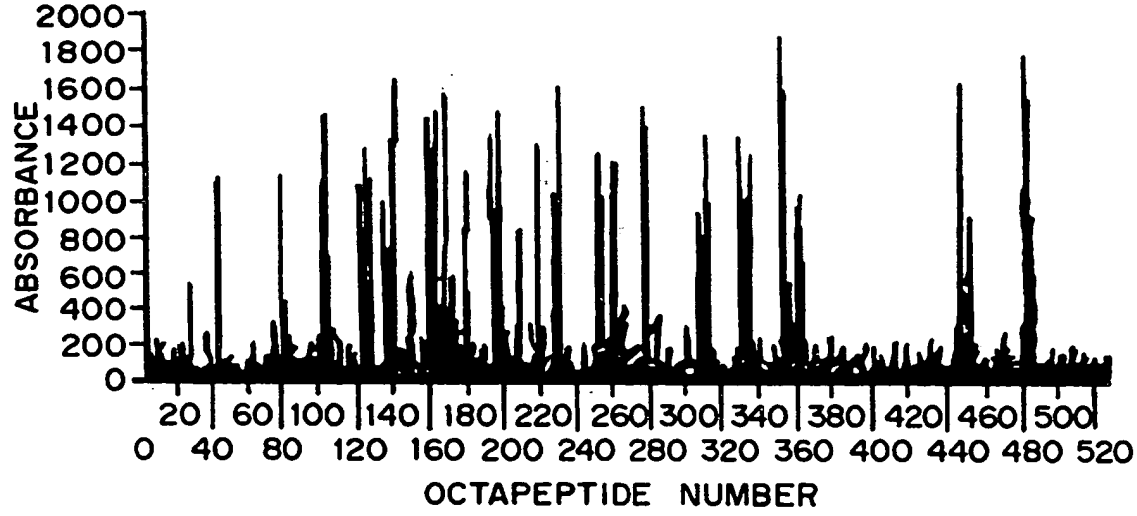

ABSORBANCE
2000
1800
1600
1400
1200
1000
800
600
400
200
0
20 60 100 140 180 220 260 300 340 380 420 460 500
40 80 120 160 200 240 280 320 360 400 440 480 520
OCTAPEPTIDE NUMBER

FIG. 7A


ABSORBANCE
2000
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20 60 100 140 180 220 260 300 340 380 420 460 500
0 40 80 120 160 200 240 280 320 360 400 440 480 520
OCTAPEPTIDE NUMBER

FIG. 7B

in any of the Sm or nRNP antigen sequences. In addition, positive control pins were synthesized from a known reactive sequence of the La/SSB peptide.

Wash steps and incubations were carried out in sealed plastic containers. Other assay steps were performed by lowering the pins into microtiter plate wells. First, pins were blocked with 3% low-fat milk in phosphate buffered saline (PBS) for one hour at room temperature. Pins were then incubated in 1:100 dilutions of sera in PBS with 0.05% Tween (PBST) and 3% milk overnight at 4° C. in humidified sealed containers. The pin blocks were then washed four times with PBST for 10 minutes each with vigorous agitation. Next, each pin was incubated with anti-human gamma chain specific IgG raised in a goat, affinity purified and conjugated to alkaline phosphatase (Jackson Immunoresearch Laboratories, West Grove, Pa.) at a 1:10,000 dilution. Para-nitrophenyl phosphate disodium was used as a substrate for alkaline phosphatase and plates were read at 405 nm with a MicroElisa™ Reader (Dynatech, Alexandria, Va.) Results for each plate were then standardized by comparison with positive control pins. The same control pins were used for all plates and were allowed to develop to a specific O.D. with a known concentration of a standard control sera.

After completion of an assay, pins were sonicated for two hours in sonication buffer (40 g sodium dodecyl sulfate, 4 ml beta-mercaptoethanol and 62.4 g sodium phosphate to 4 liters) to remove antibodies, conjugate and substrate. After sonication, pins were washed twice in hot water and boiled in methanol for 2 minutes. Pins were then allowed to air dry for a minimum of 10 minutes and were stored with desiccant or used for another assay.

Elucidation of the Major Antigenic Regions of the Sm B/B', Sm D, nRNP 70K, nRNP A and nRNP C Autoantigens

The average binding of sera containing antibodies specific for Sm B/B', Sm D, nRNP 70K, nRNP A and nRNP C are presented in FIG. 1. In virtually all of these cases the average of control sera from normals is not different from that of patients who do not have the particular specificity presented. The one exception is binding to the $(GR)_{10}$ (Sequence ID No.126) sequence of Sm D, which appears to be bound by sera from lupus patients, whether or not they have Sm or bind Sm D in immunoblot.

Forty octapeptides bound by sera with anti-Sm and anti-nRNP autoantibodies which appear to be epitopes have been identified. These are shown in Table 2. They are bound by over half of the patients with the respective Sm or nRNP autoantibodies and are bound by more than two standard deviations above controls. The absorption, inhibition and other confirmatory studies performed with representative peptides to this point are consistent with their being epitopes.

Determination of the Major Initial Anti-peptide Response of anti-Sm B/B' Systemic Lupus Erythematosus Patient Sera

Patient serum which contains both anti-Sm and anti-nRNP autoantibodies has a very homogeneous pattern of binding to the overlapping octapeptides of Sm B/B'. All patient sera tested bind five identical regions of B/B'. Four of these epitopes are proline-rich, near homologous regions: PPPGMRPP (Sequence ID No.1) (which is repeated three times in the carboxyl region of the protein) and PPPGIRGP (Sequence ID No.2). These anti-peptide responses have proven interesting in several ways.

These proline-rich, carboxyl terminal regions of Sm B/B' are the first targets of the anti-Sm response that were able to be detected in two systemic lupus erythematosus patient sera tested. FIG. 2 presents the expansion of the anti-Sm B/B' response in an anti-Sm and anti-nRNP precipitin positive patient sera over a two-year time interval. The initial response of this patient immune response is to PPPGMRPP (Sequence ID No.1) and PPPGIRGP (Sequence ID No.2). Over time this autoimmune process against Sm B/B' spreads to fifteen regions of the protein.

Second, these peptides have been synthesized in bulk (milligram quantities) on a branching poly-lysine (Map™, Applied Biosystems, Calif.) backbone. Map™ is a pyramid of fifteen lysines upon which eight peptides are added to form a multiple antigenic structure. These reagents have allowed the screening of large numbers of lupus and normal control sera. Only systemic lupus erythematosus patient sera with anti-Sm autoantibodies bind either of these sequences.

Third, these two sequences of Sm B/B' are the targets of two anti-Sm monoclonal antibodies. These murine monoclonals, developed from MRL lpr/lpr mice by David Williams of the Kennedy Institute in London, U.K., KSm 5 and KSm 3, both bind Sm B/B' in immunoblot. KSm 5 binds only the repeated PPPGMRPP (Sequence ID No.1) sequence of B/B', while KSm 3 binds the near homologous, PPPGIRGP (Sequence ID No.2) and PGIRGPPP (Sequence ID No.124) octapeptides. The binding requirements of these two monoclonals appear to be different based upon amino acid substitution and molecular modelling experiments.

Finally, antibodies directed against these peptides are not only the initial target of anti-Sm antibodies but these peptides also constitute a significant portion of the total anti-Sm response in systemic lupus erythematosus patients. Four patient sera have been absorbed over PPPGMRPP (Sequence ID No.1) and PPPGIRGP (Sequence ID No.2) columns and these anti-peptide antibodies correspond to 35 to 60% of the patient anti-Sm response. These percentages vary based upon the amount of patient serum binding to other regions of the Sm B/B' and D proteins.

The same methodology to determine the initial response to the Sm B/B' proteins in human lupus sera which contain anti-spliceosomal antibodies can also be applied to other autoantigen systems. These experiments would lead to the initial anti-peptide responses in autoantibody systems such as anti-nRNP, anti-Ro, anti-La and anti-pyruvate dehydrogenase E2 autoantigen systems, to identify a few examples.

Elucidation of the Major Antigenic Regions of the 60 kD Ro Autoantigen

The fine specificity of the anti-Ro response with the 531 overlapping octapeptides which span the 60 kD Ro protein shows varying patient sera binding patterns which share approximately sixteen regions of common binding. The quality of data in this system is comparable to that shown in FIG. 2. The studies described below further support the concept that the peptides are bound by specific autoantibodies from the lupus patients with anti-Ro autoantibodies.

Two of the major antigenic regions of 60 kD Ro which are recognized by the greatest majority of anti-Ro systemic lupus erythematosus patient sera tested are two peptides which span amino acids 274 through 292 and span amino acids 480 through 494. These sequences are presented below and have been used in rabbit immunization protocols.